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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/749,778	12/28/2000	Ranju Ralhan	041144F005	4846

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EXAMINER
SAKELARIS, SALLY A

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/749,778	RALHAN, RANJU	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-7 and 13-16* is/are pending in the application.

4a) Of the above claim(s) *1 and 8-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Arguments

Election/Restrictions

Applicant's arguments filed 9/04/02 have been fully considered but they are not persuasive. Applicant's election with traverse of Group II, claims 2-7 and 13-16 in paper No. 10 is acknowledged. The traversal is on the ground(s) that Group I, Group II and Group IV are in the same class and should be, as a result, examined together.

Inventions I and II are related as products and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the nucleic acid of invention I can be used in a materially different process such as for protein synthesis. Inventions I and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions and are not disclosed as capable of use together because the nucleic acids of invention I are not required to practice the methods of inventions IV involving polypeptides. Lastly, inventions II and IV are drawn to patentably distinct methods that involve different method steps, include different reagents and have different objectives. Invention II involves screening by genotyping through PCR with nucleic acids. Group IV is drawn to a method of pre-screening involving the use of peptide binding assays. The methods all have different method steps, objectives and reagents.

Therefore the methods are distinct over one another. Examiner reiterates that the vastly different status acquired by each group in the art would require an undue search burden including different keyword searches extending into a wide variety of databases. The restriction requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-7 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for screening subjects in the Indian, human population having or at risk of having esophageal cancer by PCR amplifying DNA isolated from either a blood, normal tissue or tumor tissue sample and assaying for the presence of the A to G polymorphism at codon 149 of the p21 waf1/cip1 gene does not reasonably provide enablement for a method for screening any subject from anywhere having or at risk of having esophageal cancer by PCR amplifying DNA isolated from any specimen or methods for genotyping cancer patients for the p21 waf1/cip1 codon 149 variant as a predictor of radiosensitivity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 2-7 and 13-16 are broadly drawn to a method for screening any subject having or at risk of having esophageal cancer by PCR amplifying DNA isolated from any specimen.

The specification teaches a method of screening human subjects from the Indian population in their finding that a significantly higher occurrence of the p21 waf1/cip1, codon 149, A to G, polymorphic variant exists in esophageal squamous cell carcinoma patients when compared to normal subjects(Pg. 8). The specification further teaches that genetic analysis of p21 waf1/cip1 was carried out in ESCC (n=50) matched esophageal normal tissues and lymphocytes from Esophageal squamous cell carcinoma(ESCC) patients as well as normal individuals (n=50)(Pg 4). The specification also teaches that this SNP resides in a cyclin dependent kinase inhibitor gene and is an important regulator of the cell cycle as it binds to PCNA and acts as a mediator of growth suppressing and apoptosis promoting functions of p53. Additionally, this codon 149 polymorphism is observed in the carboxy terminal domain of the p21 gene which is involved in PCNA binding and is described in ESCCs in a significantly higher frequency in comparison with normal individuals. The detection of this Asp/Gly substitution in ESCCs, paired normal esophageal tissues and lymphocytes in 42 of 50 cases(84%) while in a population of normal Indian individuals the occurrence of this polymorphism was observed in 8 out of the 50 cases(16%)(Pg 5). Furthermore, the specification makes reference to the present study and cites other studies in their inclusion of the Indian population as their test group. The

specification on page 5 refers to "the normal individuals in the Indian population" making up their control sample. Additionally, the specification refers to a "parallel" study on the same polymorphism that is focused on betel(the Betel plant is indigenous throughout the Indian Malay region) and tobacco related cancers as being "of immense relevance in context to the current observation." The specification does not teach the manifestation of the p21 waf1/cip1, codon 149, A to G, polymorphic variant in any population other than the Indian. The specification does not further teach the same SNP to be found from any specimen besides blood, normal tissue, and tumor tissue and even further to be found from any subject besides humans. The art also specifies that this p21 waf1/cip1, codon 149, A to G, polymorphic variant to be associated with esophageal cancer in solely the Indian population(Ralhan, 6/2000). This reference also teaches that the Indian population's Squamous cell carcinomas (SCC) come from "the commonly prevailing habit of chewing tobacco" and is a major cause of morbidity and mortality in India. In addition, the art teaches that the study's population was carefully interviewed and selected based upon their demographic, socioeconomic, occupational, and lifestyle variables, including the consumption of alcohol, betel quid, and tobacco(2441). The lack of similar detail about the present application's sample composition causes much unpredictability. The criteria previously mentioned would vary drastically depending on the subject's nationality, socio-economic status, ecosystem, tobacco use, type of tobacco use, etc. As a result, a claim drawn to a method of determining esophageal cancer in any subject from anywhere would impose undue experimentation upon the method's user.

With respect to claims 13-16, the claims are additionally, broadly drawn to a method for genotyping all cancer patients for the same p21 waf1/cip1, codon 149, A to G, polymorphic

variant as a predictor of radiosensitivity of all tumors. The specification teaches that Tian et al. 2000, showed that loss of p21 in human colon cancer cells resulted in a tremendous enhancement of radiation-induced apoptosis(Pg 4). Furthermore, the specification teaches that cancer cells with an intact p21-dependent checkpoint undergo a G1 arrest after DNA damage caused by ionizing radiation or chemotherapeutic drugs whereas cells with a defective p21 response undergo apoptosis. The specification even further teaches that p21 waf1/cip1 polymorphisms have been reported to occur more frequently in cancer patients than in healthy individuals, suggesting a role in increased susceptibility of the subject to cancer. The specification does not teach the p21 waf1/cip1, codon 149, A to G, polymorphic variant to be a predictor of radiosensitivity for tumors resulting from any cancer. It is well appreciated in the art, that cancer research is extremely complex and unpredictable; approaches that are effective for one type of cancer are not necessarily effective for other types of cancer. While the art does not teach an association with radiosensitivity, claims 13-16 are inclusive of methods that determine the degree of radiosensitivity in patients with any type of cancer with any type of cancerous tumor. However, the specification has not established that the codon 149 polymorphism is associated with the occurrence of all types of cancers. It is noted that the specification teaches an association between the codon 149 polymorphism and esophageal cancer. Additionally, while applicant's publication,(Ralhan et al. 2000), teaches an association between this polymorphism and the occurrence of oral cancer, there is no declaratory evidence of record establishing an association between the polymorphism and oral cancer. Even if declaratory evidence is provided establishing the association between the codon 149 polymorphism and oral cancer, the findings with these two cancers cannot be extrapolated to all cancers. A universal association has not

been established between the present polymorphism and all cancers and it is therefore unpredictable as to whether the codon 149 polymorphism would be associated with all types of cancers. Accordingly, the results obtained with one or two cancers cannot be extrapolated with all cancers. In this case, much unpredictability exists in the assumption that the demonstrations of Tian et al. and solely colon cancer, will follow similarly in esophageal cancers or all tumors in general. Although a similar mechanism may be used, such an extrapolation between two such different biochemical pathways would require undue experimentation to confirm.

As stated in *Vaek* (20 USPQ2d 1438), the specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to claims 2-7 and 13-16 of the present invention, one cannot readily anticipate a method for screening of any subject having or at risk of having esophageal cancer, through amplification of any specimen. One cannot anticipate what subject is being studied(ie. human, rat, Indian, Icelandic, smoker, farmer, aristocrat etc.), what specific specimen is being analyzed(ie. feces, sputum, blood, hair follicle, etc.). With respect to claims 13-16, one cannot anticipate the methods use as a predictor

of radiosensitivity of all tumors; there exits great unpredictability in speculating that different forms of cancer all behave in exactly the same way. It is noted that the claims are broadly drawn to a method for screening all subjects having or at risk of having esophageal cancer and also a method of predicting the radiosensitivity of all tumors. However, the specification only addresses a method for screening subjects in the Indian, human population having or at risk of having esophageal cancer by PCR amplifying DNA isolated from either a blood, normal tissue or tumor tissue sample that have the p21 waf1/cip1, codon 149, A to G, polymorphic variant.

With respect to the present invention, one cannot readily anticipate all subjects at risk to esophageal cancer by the use of any specimen, nor could one predict any tumors amount of radiosensitivity. Such random trial by error experimentation is considered to be undue and in view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-7 and 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 2-7 and 13-16 are rejected over the recitation of "codon 149, GAT to GGT transition,...the codon 149 polymorphic variant," as there is insufficient antecedent basis for this

limitation in the claim. In Claims 2-7 it is unclear to which "polymorphic variant" codon 149 refers. The previously mentioned codon 149 was termed to be a "transition," ie. an Adenine(purine) to Guanine(purine) alteration. The "polymorphic variant" terminology though, encompasses much more than just a transition and could refer to changes other than the transition to which this claim is meant to refer. Applicant should amend the claim to consistently term the event at codon 149 as a transition and provide adequate antecedent basis.

B. Claims 2-7 are indefinite. Claim 2 is drawn to a method of screening subjects having or at risk of having esophageal cancer. However, the final process step is one of detecting a SNP indicative of risk of cancer. Accordingly, it is unclear as to whether the claim is intended to be limited to methods of screening subjects having or at risk of having esophageal cancer or just for detecting a SNP indicative of risk of cancer as referred to in the preamble. Applicants should amend the claim to indicate how the step of screening subjects having or at risk of having esophageal cancer results in detection of a SNP being indicative of risk of cancer.

C. Claims 13-16 are indefinite. Claim 13 is drawn to a method of genotyping cancer patients as a predictor of radiosensitivity of tumors. However, the final process step is one of detecting a SNP indicative of risk of cancer. Accordingly, it is unclear as to whether the claim is intended to be limited to methods for genotyping cancer patients as a predictor of radiosensitivity of tumors or just for detecting a SNP indicative of risk of cancer as referred to in the preamble. Applicants should amend the claim to indicate how the step of genotyping cancer patients as a predictor of radiosensitivity of tumors results in the detecting a SNP indicative of risk of cancer.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 2-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Bahl et al.(Oncogene, 1/2000).

It is noted that the inventorship of the present application is distinct from the authorship of the Bahl reference . If applicable, the rejection may be overcome by the filing of a 132 Katz-type declaration.

Bahl et al. teach a method for the screening of Indian people having, or at risk of having esophageal cancer by PCR amplifying a target DNA isolated from tumor tissue with specific oligonucleotide primers. The reference further teaches purifying the PCR products followed by sequencing the products to detect a SNP in the p21 waf1/cip1 gene by determining codon 149 GAT to GGT transition(Figure 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ralhan et al.(Clinical Cancer Research, 7/2000).

It is noted that the inventorship of the present application is distinct from the authorship of the Ralhan reference . If applicable, the rejection may be overcome by the filing of a 132 Katz-type declaration.

Ralhan et al. disclose their knowledge of the method whereby esophageal cancer is detected by way of its association with the p21 waf1/cip1 gene novel polymorphism but teach(although the same method) a method for the screening of Indian people having, or at risk of having oral cancer by PCR amplifying a target DNA isolated from tumor tissue with specific oligonucleotide primers. The reference further teaches purifying the PCR products followed by sequencing the products to detect a SNP in the p21 waf1/cip1 gene by determining codon 149 GAT to GGT transition(Figure 1). The p21 waf1/cip1 gene is a universal inhibitor and polymorphic variants have been reported to occur more frequently in cancer patients than in healthy individuals suggesting a role in increased susceptibility for the development of some types of cancers. The reference teaches that high consumption of sun dried and picked vegetables, red chilies and spices in the Indian population are implicated as major predisposing factors to esophageal tumorigenesis. In addition, bidi smoking, pan chewing and pan tobacco chewing have also been identified as important risk factors for esophageal cancer in India

Ralhan does not teach the above method for the screening of Indian people having or at risk of having esophageal cancer.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Ralhan et al. so as to have included in their method a

screen for esophageal cancer as these two areas are exposed to the same major predisposing factors (ie chewing, smoking all occur first in the mouth, then in the esophagus), share the same detection method, and occur in the same population all of which would have provided a more effective method of detecting cancers of the esophagus.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Friday from 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

11/4/02

Sally Sakelaris

CARLA J. MYERS
PRIMARY EXAMINER